REMARKS/ARGUMENTS

The first paragraph of the specification has been amended to (i) include a cross-reference section heading in accordance with 37 CFR § 1.77(b)(2) and (ii) include the U.S. Patent No. 6,245,886, corresponding to the parent application, of which the present application is a divisional.

Claims 23-29 are pending in this application. Claims 26, 27, and 29 have been amended to correct obvious typographical errors. In particular, claims 26 and 29 have been amended to replace the phrase "missing a example" with the correct phrase "mixing a sample". The correct language is found in the specification, for example in originally filed claim 26. Also, claim 27 has been amended to recite "binding" instead of "biding".

Accordingly, no new matter has been added.

The Rejection of Claims 23-29 Under 35 U.S.C. § 112 ¶ 1

Claims 23-29 stand finally rejected under 35 U.S.C. § 112 ¶ 1 as not being enabled for reasons given in the June 4, 2003 Office Action. In particular, the Office Action contends that Applicants' claims are directed to *in vivo* uses that are unpredictable because of peptide stability, half-life, absorption efficiency, binding affinity, biotransformation, and clearance rate.

Applicants respectfully submit that the determination of these variables associated with *in vivo* administration is the purpose of clinical trials, such as those pursuant to obtaining FDA approval. However, the Federal Circuit has made it clear that

> FDA approval. . . is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through

> research and development, potential cures in many crucial areas such as the treatment of cancer.

In re Brana, 51 F.3d. 1560, 1568 (Fed. Cir. 1995) (emphasis added). As such, Applicants' claims, directed to a method of treatment, are enabled without the need to demonstrate clinical efficacy, as required for FDA approval.

The Office Action further contends that Applicants' examples cannot be construed as "proper working examples," without evidence that Applicants' *in vitro* assay data correlates with treating a claimed condition. According to the Office Action's further reasoning, the claims are not enabled without "proper working examples". Regarding the requirement for correlation between *in vitro* and *in vivo* activity, the Federal Circuit has held that

> Of course, it is possible that some compounds active *in vitro* may not be active *in vivo*. But as our predecessor court in Nelson explained, a "rigorous correlation" need not be shown in order to establish practical utility; "reasonable correlation" suffices.

Fujikawa v. Wattanasin, 93 F.3d 1559, 1565 (Fed. Cir. 1996) (emphasis added).

In view of the above, Applicants submit that claims 23-29 are enabled because their own specification provides ample evidence of a well-documented correlation between (1) the loss of p53 DNA binding activity, which is measured in the Applicants' assay model, and (2) the propensity for humans to develop tumors. Specifically, the paragraph bridging pages 1 and 2 of Applicants' specification states:

> In more than half of all human tumors, the gene encoding p53 is mutated [Harris (1993), cited above]. Thus, the encoded mutant p53 protein is unable to bind DNA [Bargonetti *et al.* (1992), Genes Dev., 6: 1886-1898] and perform its tumor suppressing function. The loss of p53 function is critical for tumor development. Introduction of wild-type p53 into tumor cells leads to the arrest of cell proliferation or cell death [Finlay *et al.* (1989), Cell, 57: 1083-1093; Eliyahu *et al.* (1989), Proc. Natl. Sci. USA, 86: 8763-8767; Baker *et al.* (1990), Science, 249: 912-915; Mercer *et al.* (1990), Proc. Natl. Acad. Sci. USA, 87: 6166-6170; Diller *et al.* (1990), Mol. Cell. Biol., 10: 5772-5781; Isaacs *et al.* (1991), Cancer Res., 51: 4716-4720; Yonish-Rouach *et al.* (1993), Mol. Cell. Biol., 13: 1415-1423; Lowe *et al.* (1993), Cell, 74: 957-967; Fujiwara *et al.* (1993), Cancer Res., 53: 4129-4133; Fujiwara *et al.* (1994), Cancer Res., 54: 2287-2291].
> (emphasis added)

From the above-quoted passage, there is a vast amount of literature evidencing the relationship between the DNA binding functionality of wild-type p53 (measured in Applicants' *in vitro* assay procedure described on pages 23-24 the specification) and the ability of wild-type p53 (*i.e.*, p53 having the requisite DNA binding functionality) to suppress tumors *in vivo*.

Additionally, if the above information is not sufficient, more recent studies also verify this correlation. For example, Luo *et al.* recognize, "[t]he high prevalence and great diversity of p53 tumor suppressor gene mutations in human tumors call for development of therapeutic molecules that rescue the function of aberrant p53 protein." [*see* abstract of Oncogene. 2001 Jan 18;20(3):320-8, copy enclosed] (emphasis added). Luo *et al.* describe studies using a genetically modified mouse p53 protein (*i.e.*, hupki p53 protein) having a core domain matching the polypeptide sequence of human p53.[1] Luo *et al.* report that mice expressing the hupki p53 protein (which binds DNA in the gel mobility shift assay) "do not develop spontaneous tumors at an early age, in contrast to. . . [mouse] strains with a defective p53 gene." Therefore, Luo *et al.*, provide yet further evidence that efficacy in Applicants' *in vitro* assay model correlates directly to efficacy for the treatment of cancer *in vivo*.

Based on the above evidence, the art clearly recognizes Applicants' *in vitro* assay model (activation of p53 binding to DNA) as correlating to the *in vivo* treatment of cancer. According to MPEP § 2164.02, therefore, this assay model "should be accepted as correlating unless the Examiner has evidence that the model does not correlate." (emphasis added). Applicants respectfully submit that general physiological uncertainties (*i.e.*, pharmacokinetics, stability, bioabsorption, clearance rate, *etc.*) offered in the June 4, 2003 Office Action do not provide the required specific evidence necessary to assert that Applicants' p53 DNA binding assay does not

[1] Luo *et al.* report, "[t]he hupki p53 protein binds to p53 consensus sequences in gel mobility shift assays. . ." Interestingly, gel mobility shift assays are the same assays that Applicants describe on pages 23-34 (under the heading "Assay Procedure"), in which test proteins are incubated with oligonucleotide containing a p53 binding site (*i.e.*, a consensus sequence).

correlate with the treatment of cancer. As such, the reasons given in the June 4, 2003 Office action do not constitute the legally-required objective evidence necessary to rebut Applicants' presumption of enablement. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

Notwithstanding the above failure of the Office Action to provide specific reasons why the model does not correlate, Applicants submit that there are currently many types of polypeptide pharmaceutical agents that are administered to humans and that also exhibit the pharmacokinetics, stability, bioabsorption, clearance rate, etc., necessary for therapeutic efficacy. Erythropoietin and cytokines come to mind as major examples. The enclosed abstracts of recently-published articles by Macdougall and Vilcek *et al.*, report on the success of administering these protein molecules, despite any initial or even ongoing studies to address uncertain physiological variables.

For all of the above reasons, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, ¶ 1.

CONCLUSION

Accordingly, in view of the above amendments and remarks, Applicants submit that claims 23-29 are patentable and respectfully request a written indication of their allowance.

Respectfully submitted,

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Enclosures:

(1) Notice of Appeal
(2) Luo *et al.* Oncogene. 2001 Jan 18;20(3):320-8 (abstract)

1: Oncogene. 2001 Jan 18;20(3):320-8. Related Articles, Link

nature publishing group

Knock-in mice with a chimeric human/murine p53 gene develop normally and show wild-type p53 responses to DNA damaging agents: a new biomedical research tool.

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The high prevalence and great diversity of p53 tumor suppressor gene mutations in human tumors call for development of therapeutic molecules that rescue function of aberrant p53 protein. P53 mutations also offer new approaches to the study of the origins of mutations in human cancer. An experimental mouse model with a genetically modified but normal functioning p53 gene harboring the human rather than the murine core domain, would be of considerable benefit to research on both cancer therapeutics and etiology; however, it is uncertain whether such mice would permit biological functions of p53 to be retained. Using a Cre/lox P gene-targeting approach, we have constructed a human p53 knock-in (hupki) mouse strain in which exons 4-9 of the endogenous mouse p53 allele were replaced with the homologous, normal human p53 gene sequence. The chimeric p53 allele (p53(KI)) is properly spliced, transcribed in various tissues at levels equivalent to wild-type mice, and yields cDNA with the anticipated sequence, that is, with a core domain matching that of humans. The hupki p53 protein binds to p53 consensus sequences in gel mobility shift assays and accumulates in the nucleus of hupki fibroblasts in response to UV irradiation, as is characteristic of wild-type p53. Induction of various p53-regulated genes in spleen of gamma-irradiated homozygous hupki mice (p53 (KI/KI)), and the kinetics of p53-dependent apoptosis in thymocytes are similar to results with wild-type (p53(+/+)) mice, further indicating normal p53 pathway function in the hupki strain. The mice are phenotypically normal and do not develop spontaneous tumors at an early age, in contrast to knock-out (p53(-/-)) strains with a defective p53 gene. The chimeric (p53(KI)) allele thus appears to provide a biological equivalent to the endogenous murine (p53 (+)) gene. This strain is a unique tool for examining in vivo spontaneous and induced mutations in human p53 gene sequences for comparison with

published human tumor p53 mutation spectra. In addition, the hupki strain paves the way for mouse models in pre-clinical testing of pharmaceuticals designed to modulate DNA-binding activity of human p53.

PMID: 11313961 [PubMed - indexed for MEDLINE]
